# Mechanisms of abiotic degradation and soil–water interactions of pesticides and other hydrophobic organic compounds. Part 3. Nucleophilic displacement at the phosphorus centre of the pesticide fenitrothion [*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate] by oxygen nucleophiles in aqueous solution: α-effect and mechanism †

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Rate constants for the reaction of the title compound, **1**, with a number of oxygen nucleophiles, including structurally related phenoxides and oxygen-based α-nucleophiles, have been measured in aqueous solution at 25 °C. A significant α-effect was observed, confirming participation of the nucleophile in the rate-limiting step of the reaction as well as indicating different transition states (TS) for the reaction of α-nucleophiles compared to normal ones. The Brønsted-type correlation of log $k_{Nu}$ *vs.* p$K_a$ of nucleophiles shows a linear plot for the series of structurally related phenoxides in the p$K_a$ range 5.4–10.0, straddling the p$K_a$ of the leaving group (3-methyl-4-nitrophenoxide, p$K_a$ 7.20), but is curved in the highly basic region corresponding to $CF_3CH_2O^-$ and $HO^-$ as nucleophiles. The slope of the linear portion of the plot ($\beta_{Nu}$) is 0.49 ($R^2$ 0.988). The linearity of the plot for the series of structurally related phenoxides is consistent with a concerted mechanism for nucleophilic attack at the P center of the substrate. A value of $\beta_{lg}$ −0.39 ($R^2$ 0.973) is measured for the reaction of $PhO^-$ with substituted phenyl dimethyl phosphorothioate esters. Combining the values of $\beta_{Nu}$ and $\beta_{lg}$ gives $\beta_{eq}$ = 0.88; these parameters when considered together with the effective charge distribution in the TS, demonstrate that the TS for the symmetrical reaction (in which nucleophile = leaving group = 3-methyl-4-nitrophenoxide) has no significant phosphorylium ion character. The Leffler index points to a concerted reaction in which bond formation is slightly ahead of bond rupture in the TS. Data from the present study are compared with literature data for (thio)phosphoryl group transfer. We propose that, unless special structural and/or environmental features prevail, (thio)phosphoryl transfers between phenoxides are more likely to occur *via* a concerted mechanism. It is shown that the TS for the concerted transfer of $(EtO)_2P{=}O$ between two $PhO^-$ moieties shows more pentacoordinate intermediate character than the symmetrical reaction of **1** due to differences in (i) basicity of $PhO^-$ *versus* 3-$CH_3$,4-$NO_2PhO^-$, and (ii) abilities of O and S in the P=X (X = O, S) moiety to stabilize the incoming negative charge.

## Introduction

While the vital role of organophosphorus and other classes of pesticides in increasing the world's food supplies over the last five decades is firmly established,[1a] the possible toxicity to humans and long-term environmental effects[1b] dictate that thorough and in-depth studies of their degradation mechanisms be undertaken. To that end we have initiated studies on the mechanism of abiotic degradation and soil–water interactions of pesticides and other hydrophobic organic compounds, with the ultimate goal of providing rate data to aid in the assessment of the stability and persistence of these compounds in the environment.

Fenitrothion, *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate, **1**, has found use as a broad spectrum insecticide and acaricide,[2a] efficacious in controlling a range of orchard, forest and field crop pests. It is also classified as an anti-acetylcholinesterase neurotoxin.[2b] Hence the chemistry of **1** is important to a broad range of interests.

The present paper examines the nucleophilic reaction of a variety of oxygen nucleophiles at the P center of **1** in water at 25 °C. It is noted that a variety of species which can function as oxygen nucleophiles abound in the aquatic, terrestrial and atmospheric environment. This study also seeks to contribute to ongoing discussion on the detailed mechanism of phosphoryl transfer reactions which occupy a central role in the biochemistry of life processes.

Phosphates of nucleotides and other phosphorylated compounds are energy-carriers in biological systems, while phosphorylation of proteins and enzymes is crucial to control mechanisms.[3–5] Genetic engineering techniques are critically dependent on the selective fission of phosphodiester bonds.[5a] A new phosphoryl transfer process involving 1,3-diols has been suggested, consequent upon the discovery of RNA enzymes (ribozymes).[3] As a consequence of the importance of phosphate esters and phosphoryl transfer reactions in nature, continuing interest has attached to elucidation of the mechanisms of nucleophilic displacements at P centers.[5–9] Comparisons of data for acyl, carbonyl, sulfyl transfers and identity as well as elimination reactions, with those of phosphoryl

† For Part 2, see ref. 52.

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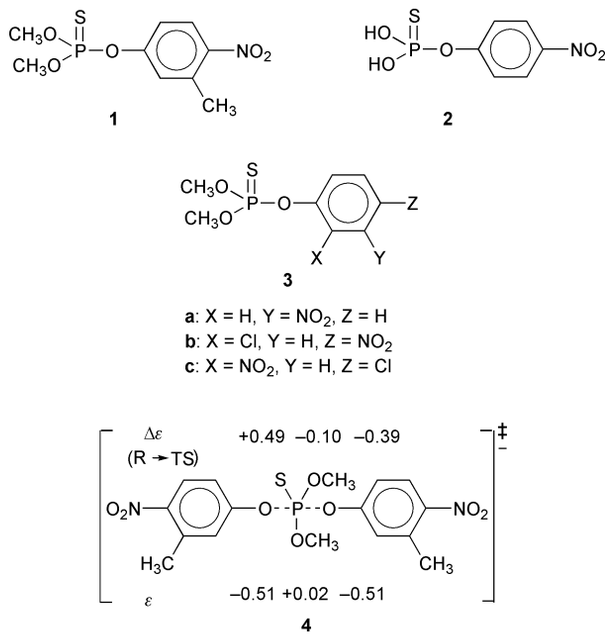



transfers, continue to enhance our understanding of bond-making and bond-breaking processes in organic/biochemical reactions, especially in relation to what constitutes the rate-limiting step and whether or not these processes are concerted.[5–8,10–12]

Under certain reaction conditions, evidence exists for metaphosphate and metaphosphate-like intermediates in phosphoryl group transfers and related reactions.[13,14] Jencks has shown[5d] that the transition state for phosphoryl transfer to anionic oxygen nucleophiles from pyridine is dissociative and metaphosphate-like, showing less dissociative character with increasing basicity of the oxygen nucleophile or the pyridine leaving group. The solvolysis of the mono/dianion of chiral *p*-nitrophenyl [$^{18}$O,$^{16}$O]phosphorothioate shows significant racemization, thus implicating the formation of a free thiometaphosphate intermediate.[15] Stereochemical evidence from the nonenzymic hydrolysis of deoxyadenosine 5′-[β-$^{17}$O]-β-thiodiphosphate in $H_2{}^{18}O$ at pH 4.5 indicates that this process also occurs with partial racemization.[15d] Alkoxyphosphoranes and (aryloxy)phosphoranes, which are pentacoordinate phosphorus derivatives, and similar species have been demonstrated as intermediates in phosphyl group transfers between strong nucleophiles.[13d,14b] On the other hand, results from stereochemical probes of mechanism[16] and the work of Williams and co-workers,[6,7] the latter using Brønsted-type dependence on nucleophile p$K_a$ and parameters derived therefrom as criteria of mechanism, have demonstrated concertedness in phosphoryl/phosphyl group transfers in which case both nucleophile entry and leaving group departure occur in a single transition state.

There is also the notion that whereas the formation of a metaphosphate intermediate is facilitated by the absence of competent potential acceptors, thiophosphate transfers in solution could routinely occur *via* thiometaphosphate intermediates.[3b] This view is predicated on the perceived greater stability of thiometaphosphate over metaphosphate, which receives experimental support in the gas phase detection of the former[20] and the isolation of trithiometaphosphate as its tetraphenylarsonium salt.[21] Rate and stereochemical differences between nucleophilic substitution reactions of phosphates and phosphorothioates have aided the inference of mechanistic information regarding enzymic catalysis of phosphoryl transfers.[3] The recent work of Hengge[3b] on the hydrolysis of mono- and dianions of *p*-nitrophenyl phosphorothioate, **2**, provides interesting and significant information on phosphorothioate reactivity and mechanism of reaction.

**Table 1** Second-order rate constants ($k_{Nu}$) for the attack of several oxygen nucleophiles at the phosphorus center of **1** in water at 25 °C

| Entry | Nucleophile | p$K_a$[a] | $k_{Nu}/10^{-5}$ M$^{-1}$ s$^{-1}$[b] |
|---|---|---|---|
| 1 | $HO^-$ | 15.74 | 279.0 |
| 2 | $CF_3CH_2O^-$ | 12.4 | 44.7 |
| 3 | $HOO^-$ | 11.6 | 59 300 |
| 4 | $PhO^-$ | 9.99 | 79.8 |
| 5 | $Ox^-$[c] | 9.44 | 180.0 |
| 6 | 4-$ClPhO^-$ | 9.38 | 4.88 |
| 7 | 4-$CNPhO^-$ | 7.72 | 0.561 |
| 8 | 2,4,5-$Cl_3PhO^-$ | 6.70 | 0.298 |
| | | | 0.316 |
| 9 | 2,3,5,6-$F_4PhO^-$ | 5.53 | 0.048 |
| | | | 0.052 |

[a] Values of the p$K_a$'s for the conjugate acids of the nucleophiles at 25 °C, obtained from the literature. [b] Each rate constant is the average of duplicate runs with a deviation of ±3%; data for 2,4,5-$Cl_3PhO^-$ were obtained by the initial rate method (see text and ref. 51) and are subject to an uncertainty of ±5%. [c] $Ox^-$ = butane-2,3-dione monoximate.

There has been no report, to our knowledge, of a study of nucleophilic displacement in phosphorothioate esters by a series of structurally related phenoxides which forms the pivot of the present paper. Such studies involving structurally related phenoxides of pyridines have been reported for phosphates and similar substrates.[5d,7] Data from the present paper are subjected to Williams' method[6,7] for elucidating mechanisms of nucleophilic displacements which has so far not been applied to phosphorothioate substrates. The nucleophiles employed in this study include some α-nucleophiles, with a view to ascertaining whether the reaction of interest exhibits an "α-effect".[17] Observation of the α-effect is a satisfactory criterion for establishing the participation of the nucleophilic species in the rate-limiting step of a bimolecular displacement reaction.[17–19]

Our results provide kinetic data for attack of oxygen-based nucleophiles on the pesticide **1** and extend information available for these processes at the P center. By comparison with existing literature data, these results provide greater latitude for discussing (thio)phosphoryl transfers. Significantly, a concerted mechanism in which bond-making is slightly ahead of bond rupture is established in the transition state for the symmetrical reaction of **1**.

## Results

First-order rate constants, $k_{obs}$, for the reaction of **1** with a number of oxygen nucleophiles, to include the α-nucleophiles hydroperoxide ($HOO^-$) and butane-2,3-dione monoximate ($Ox^-$), have been measured spectrophotometrically under pseudo first-order conditions in water at 25 °C, with the nucleophiles in large excess over the substrate in each case. The corresponding second-order rate constants were evaluated from plots of $k_{obs}$ *vs.* [Nu], which were linear in all cases. The results, together with p$K_a$'s of the conjugate acids of the nucleophiles employed, are presented in Table 1. A Brønsted-type plot of log $k_{Nu}$ *vs.* p$K_a$ of the conjugate acid of the nucleophile, using the data of Table 1, is displayed as Fig. 1.

Eqn. (1) describes the reaction of **1** with nucleophiles; $k_o$ defined in eqn. (2) corresponds to the intercept in the $k_{obs}$ *vs.* [Nu] plot.

$$k_{obs} = k_o + k_{Nu}[Nu] \quad (1)$$

$$k_o = k_{H_2O} + k_{HO^-}[HO^-] \quad (2)$$

The $k_{H_2O}$ term may assume some significance for very weak nucleophiles and at very low $HO^-$ concentrations. At high pH, the intercept, if present, is dominated by the $k_{HO^-}$ term. These situations apply provided the intercept is significant in

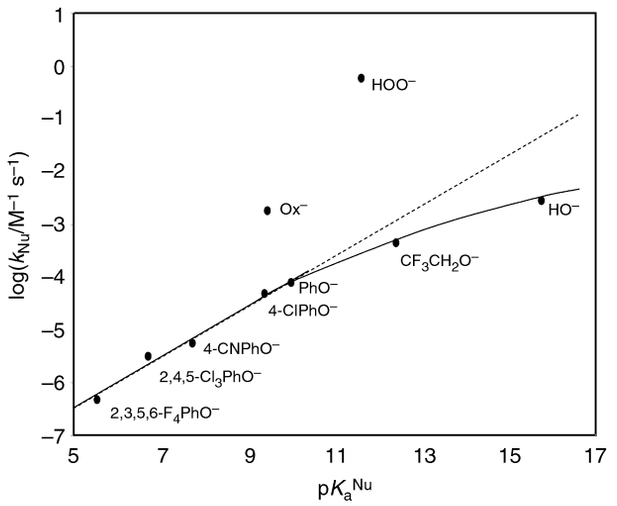



**Fig. 1** Plot of log $k_{Nu}$ *vs.* p$K_a$ (nucleophile) for the reaction of **1** with oxygen nucleophiles in water at 25 °C.

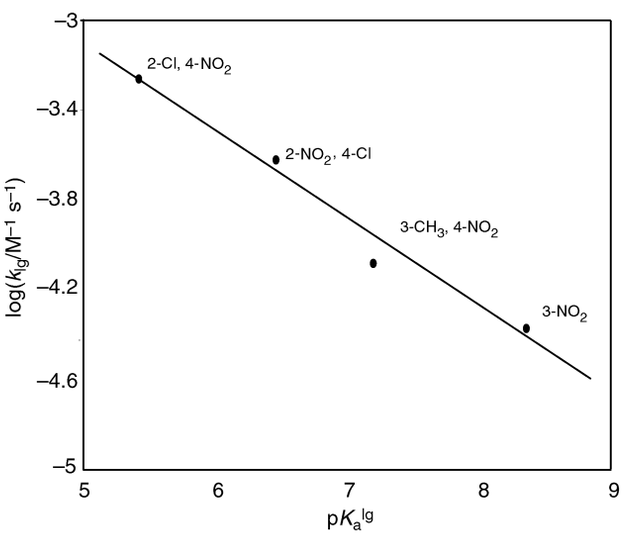



**Fig. 2** Plot of log $k_{lg}$ *vs.* p$K_a$ (leaving group) for the reaction of $PhO^-$ with **1** and **3a–c** in water at 25 °C. The line is defined by eqn. (4).

comparison to the associated experimental error. Significant intercepts were observed in the plots of eqn. (1) for the nucleophiles $CF_3CH_2O^-$, 4-$ClPhO^-$, 4-$CNPhO^-$, 2,4,5-$Cl_3PhO^-$ and $Ox^-$ but not for $HO^-$, $HOO^-$, $PhO^-$ and 2,3,5,6-$F_4PhO^-$.

Polar substituent effects in nucleophilic attack at the P center of **1** were evaluated by keeping the attacking nucleophile ($PhO^-$) constant while varying the leaving group by altering the substituents on the leaving group phenyl moiety. Thus the rates of the reaction of **1** and **3a–c** with $PhO^-$ were investigated under pseudo first-order conditions at 25 °C. The relevant second-order rate constants are assembled in Table 2. Construction of a Brønsted-type dependence of log $k_{lg}$ *vs.* p$K_a$ of the conjugate acid of the leaving group results in the linear plot of Fig. 2.

## Discussion

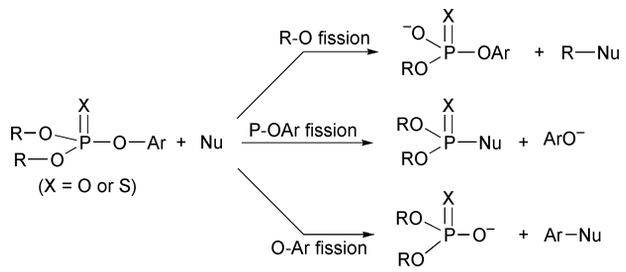
### (i) Reaction pathways for nucleophilic attack on 1

Scheme 1 displays the three possible pathways for the attack of nucleophiles on **1** and similar substrates. Fission of P–OAr and Ar–O bonds, occurring at comparable rates, was observed by Kirby and Younas[19a] in the reaction of methyl 2,4-dinitrophenyl phosphate monoanion with oxyanions in water; the latter reaction is an $S_NAr$ displacement. The $S_NAr$ (Ar–O fission) pathway has also been demonstrated[23] in the aminolysis

**Table 2** Second-order rate constants ($k_{lg}$) for the reaction of $PhO^-$ with a series of substituted dimethyl phosphorothioates in water at 25 °C

| Substrate | Leaving group | p$K_a$[a] | $k_{lg}/10^{-5}$ $M^{-1}$ $s^{-1}$[b] |
|---|---|---|---|
| **3a** | 3-$NO_2$-$PhO^-$ | 8.36[c] | 4.22 |
| **1** | 3-$CH_3$,4-$NO_2$-$PhO^-$ | 7.20[d] | 8.23 |
| **3c** | 2-$NO_2$,4-Cl-$PhO^-$ | 6.46[c] | 24.1 |
| **3b** | 2-Cl,4-$NO_2$-$PhO^-$ | 5.42[c] | 54.9 |

[a] Values for the p$K_a$'s of the conjugate acids of the leaving groups, obtained from the literature. [b] Estimated error ±3%. [c] See ref. 5*b*. [d] See ref. 22.




**Scheme 1**

of *p*-nitrophenyl phosphate. By contrast, the reaction of 2-(2,4′-dinitrophenyl)-2-oxo-1,3,2-dioxaphosphinanes with various oxygen nucleophiles in water gives P–OAr fission products only.[19b] Hydrolysis of **1** has been shown[24] to proceed by Me–O bond fission at low pH (≤ 7.5) and exclusively by way of P–OAr fission at high pH (> 9).

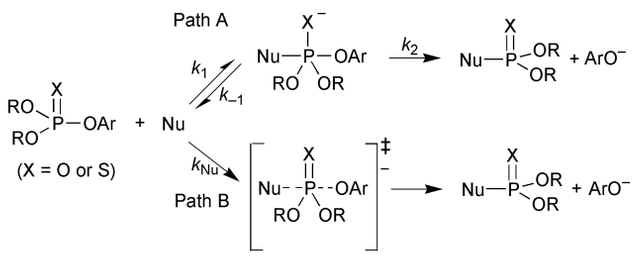
The present study was undertaken in buffered systems in the pH range 8.5–12.4. No products of Me–O fission were observed by $^{31}P$ NMR spectroscopy, consistent with the observation that Me–O fission is insignificant in this region.[24] The experimental absorbances of 3-methyl-4-nitrophenoxide measured at infinite reaction times for the reactions of entries 1–7 in Table 1 agreed with theoretical values. For the nucleophiles 2,4,5-$Cl_3PhO^-$ and 2,3,5,6-$F_4PhO^-$ whose rates were determined by the initial rate method, corresponding NMR experiments did not identify products of Me–O or Ar–O fission. We conclude, therefore, that the reaction of **1** with the nucleophiles listed in Table 1 proceeds through P–OAr fission. It is noted, however, that the $S_NAr$ (Ar–O fission) pathway is an important process in the aminolysis of **1**.[25]

### (ii) α-Effect

Data in Table 1 and Fig. 1 show that $k_{Nu}$ values for the α-nucleophiles $HOO^-$ and $Ox^-$ are higher than the corresponding ones for reactions involving normal O-nucleophiles of similar p$K_a$. One can estimate from Fig. 1 that $HOO^-$ and $Ox^-$ behave like nucleophiles with p$K_a$ values of ~ 17.5 and 12.7 rather than their actual p$K_a$ values of 11.6 and 9.4, respectively. Rate constant ratios comparing reactivities of α- and normal nucleophiles, $k^\alpha/k^n$, of 37 and 1300 for the pairs $Ox^-$/4$ClPhO^-$(p$K_a$'s 9.44, 9.38) and $HOO^-/CF_3CH_2O^-$ (p$K_a$'s 11.6, 12.4), respectively, demonstrate the magnitude of the α-effect observed in this study. The α-effect of 1300 observed for the $HOO^-/CF_3CH_2O^-$ pair conceivably incorporates solvation factors at play in the reactivity of strongly basic anions noted below.

A number of studies have demonstrated the α-effect in nucleophilic attack at the P centre.[5c,7,17i,26,27] The magnitude of the α-effect reported in pure water for oxygen nucleophiles reacting at a P centre is 15 for the $Ox^-$/4-$ClPhO^-$ pair[17i] and in the range of 10–200 for the $HOO^-/HO^-$ pair.[27] A value of 210 is calculated for the $HOO^-/HO^-$ pair from data in Table 1, in good agreement with the range reported previously.[27] We note, however, that the magnitude of the α-effect is substrate-dependent.

Although a consensus on the origin of the α-effect is lacking,[5c,28] it is considered that the transition-state structure for reactions of the α-nucleophile is very different from that for the reactions of the normal nucleophile.[5c,17j] The inference that can be drawn from the present results is that the reaction of **1** with nucleophiles proceeds through either a two-stage mechanism with rate-limiting formation of the pentacoordinate intermediate or a one-step concerted mechanism, as shown in Scheme 2. The alkaline hydrolysis of $Ph_2P(S)$–OPhX correlates




**Scheme 2**

well with Hammett σ-values which suggests that formation of a pentacoordinate intermediate is rate-determining;[29] however, no definitive exclusion of an alternative concerted mechanism with an early TS and minimal leaving group separation was achieved in that system.

### (iii) Brønsted-type correlations: $\beta_{Nu}$ and $\beta_{lg}$ values

Brønsted-type correlations probe the properties of the transition states of reactions,[30–33] and have proved an invaluable tool for elucidating the mechanisms of nucleophilic displacements at various electrophilic sites.[5–11] For a series of structurally related nucleophiles, particularly those with the same atom at the nucleophilic site, Brønsted $\beta_{Nu}$ and $\beta_{lg}$ values are useful in estimating transition structures and evaluating their response to changing substitution patterns and reaction conditions.[6,31]

The traditional Brønsted-type plot of log $k_{Nu}$ *vs.* p$K_a$ depicted in Fig. 1 can now be discussed. Inspection of Fig. 1 reveals that the plot is linear for nucleophiles with p$K_a$ < 11 while curvature at higher p$K_a$'s is clearly evident. The curvature at high p$K_a$ is consistent with Jencks' observation[5e,11a] that the reactivity of $HO^-$ and strongly basic alkoxides is characteristically low due to abnormal solvation of these anions relative to the more weakly basic phenolate anions, rather than a change in the rate-determining step.

If the points for $HO^-$ and $CF_3CH_2O^-$ are excluded, it is seen that requirements for a valid Brønsted-type plot, *i.e.* structural similarity of nucleophiles and a p$K_a$ range that straddles the basicity of the leaving group, are satisfied by the group of phenoxides listed in Table 1. The solid line defined by the phenoxides up to $PhO^-$ (p$K_a$ 10.0) is given by eqn. (3) from

$$\log k_{Nu} = (0.49 \pm 0.01)pK_a - 8.94 \pm 0.04 \qquad (3)$$

which $\beta_{Nu} = 0.49 \pm 0.01$ ($R^2$ 0.988) is obtained. The value of 0.49 for $\beta_{Nu}$ can be compared with $\beta_{Nu} = 0.53$ and 0.46 obtained from the reaction of phenoxides with 4-nitrophenyl diphenyl phosphate $(PhO)_2P(O)$–OPhX,[7a] and 4-nitrophenyl diphenylphosphinate $Ph_2P(O)$–OPhX,[7b] respectively in aqueous solution at 25 °C; these reactions have been unambiguously shown to proceed *via* the concerted mechanism.

Eqn. (4) defines the straight line obtained from the plot of log $k_{lg}$ *vs.* p$K_a$ (Table 2, Fig. 2), giving $\beta_{lg} = -0.39 \pm 0.04$ ($R^2$ 0.973). This can be compared with $\beta_{lg}$ values of −0.87, −0.79,

$$\log k_{lg} = (-0.39 \pm 0.04)pK_a - 1.16 \pm 0.08 \qquad (4)$$

−0.51, and −0.64 obtained for the reaction of $PhO^-$ with $(PhO)_2P(O)$–OPhX,[7a] $Ph_2P(O)$–OPhX,[7b] $(EtO)_2P(O)$–OPhX,[34] and the monoanion of MeO(OH)P(O)–OPhX,[34] respectively, in water. Clearly, these latter substrates are more sensitive to polar effects and exhibit greater leaving group separation in the TS of their reactions with phenoxides than **1**. The value of $\beta_{lg} = -0.39$ compares with −0.30 obtained for the hydrolysis of $Me_2P(S)$–OPhX[35] in water at 25 °C, and lies within the range of $\beta_{lg} = -0.30$ to −0.50 observed[35,36] for the hydrolysis of $Me_2P(S)$–OPhX, MePhP(S)–OPhX, and $Ph_2P(S)$–OPhX in 50% ethanol at 25 °C. These latter P=S substrates studied by Istomin and co-workers,[35,36] as well as **1**, appear to exhibit a lesser degree of bond cleavage in the TS of their reactions with phenoxides than the P=O substrates reported by Williams and co-workers.[7,34] The values of $\beta_{Nu}$ and $\beta_{lg}$ combined with $\beta_{eq}$ for the P=O substrates studied by Williams and co-workers reveal a concerted mechanism in which there is (i) more advanced bond cleavage than bond-making in the TS for $Ph_2P(O)$–OPhX, such that the $Ph_2P(O)$ group acquires a positive character;[7b] (ii) a TS for $(EtO)_2P(O)$–OPhX that has more pentacoordinate intermediate character than the reaction of $Ph_2P(O)$–OPhX;[7a,34] and (iii) a slight charge imbalance in the TS which results in some phosphorylium ion character for $(PhO)_2P(O)$–OPhX.[7a] By contrast, Hollfelder and Herschlag[37] found a value of $\beta_{lg} = 1.1$ for the hydrolysis of *O*-aryl phosphorothioate dianions, similar to the value of −1.2 reported for their phosphate ester counterparts;[38] this suggests a very small amount of P–O bonding in the TS. Such a TS is dissociative in character, resembling the (thio)metaphosphate intermediate. The salient point here is that the $\beta_{lg}$ value for **1** differs radically from that reported for *O*-aryl phosphorothioate dianions.[37] Comparing P=O and P=S substrates, we note that the $\beta_{Nu}$ value for **1** is similar to the values reported for $(PhO)_2P(O)$–OPhX[7a] and $Ph_2P(O)$–OPhX,[7b] while the $\beta_{lg}$ value for **1** differs substantially from the values obtained for $(PhO)_2P(O)$–OPhX,[7a] $Ph_2P(O)$–OPhX,[7b] and the monoanion of MeO(OH)P(O)–OPhX[34] but is in the same range as $\beta_{lg}$ values for $Me_2P(S)$–OPhX,[35] MePhP(S)–OPhX,[35,36] and $(EtO)_2P(O)$–OPhX.[34]

### (iv) Mechanism, effective charge distribution and transition-state structure

A mechanism involving a distinct thiometaphosphate intermediate is untenable in the present case since the observation of an α-effect implies participation of the nucleophile in the rate-limiting step of the reaction. The linear portion of the plot in Fig. 1 for the phenoxides shows that their reaction with **1** proceeds by a concerted [$S_N2$(P) type] mechanism with a single transition state (see Path B, Scheme 2). Although the data do not unequivocally rule out the presence of a highly reactive pentacoordinate intermediate lying in a shallow well at the energy maximum in the reaction coordinate,[7] we will show below, using the reaction map of Fig. 3, that such an intermediate would be too unstable to have any real existence.

The effective charge on the entering and leaving O atoms in the TS of a concerted reaction can be determined from the values of $\beta_{eq}$, defined according to eqn. (5), $\beta_{Nu}$, and $\beta_{lg}$,

$$\beta_{eq} = \beta_{Nu} - \beta_{lg} \qquad (5)$$

according to the methodology of Williams[6,7] and Jencks.[5b–d] Two conditions are required to establish the validity of eqn. (5): (i) reactions yielding the values of $\beta_{Nu}$ and $\beta_{lg}$ must be the microscopic reverse of each other; and (ii) the same rate-limiting step is involved in measurement of both quantities. We believe the system under study satisfies both requirements. The effective charge on O of the attacking nucleophile and O of the leaving group in going from the ground state to the TS, $\Delta\varepsilon(R \rightarrow TS)$, is taken to be equal to $\beta_{Nu}$ (0.49) and $\beta_{lg}$ (−0.39), respectively. The charge imbalance of +0.10 between attacking and leaving O (see structure **4**) is probably balanced by −0.10 charge unit from the thiophosphoryl group in order to maintain

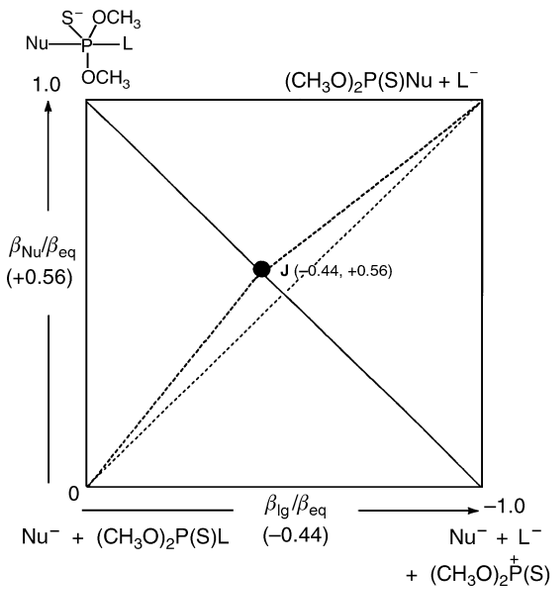



**Fig. 3** Reaction map for the transfer of the dimethylthiophosphoryl group between nucleophile and aryloxide leaving groups. Bond formation and bond fission are measured by $\alpha_{bf} = \beta_{Nu}/\beta_{eq}$ and $\alpha_{br} = \beta_{lg}/\beta_{eq}$, respectively (see text). The point J represents the position of the TS for the symmetrical reaction in which nucleophile = leaving group = 3-methyl-4-nitrophenoxide.

overall charge neutrality. $\beta_{eq}$ in the present system is +0.88; this represents the overall charge change on the nucleophile and leaving group for the overall reaction. In the ground state, therefore, the phenoxy O will have a charge of −0.12. The effective charge on the nucleophilic O in the TS, $\varepsilon_{TS}$, is given by eqn. (6),

$$\varepsilon_{TS} = \beta_{Nu} + \varepsilon_{R} \quad (6)$$

in which $\varepsilon_{R}$ is the charge on the nucleophile in the ground state which is −1.0; for the present system, $\varepsilon_{TS} = -0.51$.

The Leffler index,[32] $\alpha'$, measures the extent of bonding in the TS for any particular bond.‡ The extent of bond formation, $\alpha'_{bf} = \beta_{Nu}/\beta_{eq}$, and the extent of leaving group bond rupture, $\alpha'_{br} = \beta_{lg}/\beta_{eq}$, are calculated to be 0.56 and −0.44, respectively. These values of $\alpha'_{bf}$ and $\alpha'_{br}$ locate the position of the TS in the reaction map (Fig. 3) as J along the tightness diagonal[39] or disparity reaction,[31] only slightly displaced from the intersection of the synchronous route and the tightness diagonal, thus confirming that the reaction under consideration is a concerted one in which bond formation is only slightly advanced over bond rupture in the TS. This result is inconsistent with the presence of a discrete pentacoordinate intermediate, since such an intermediate will be too unstable to have any real existence at this point of the energy surface. Structure **4** shows the charge distribution for the symmetrical reaction with 3-methyl-4-nitrophenoxide as entering and leaving group, for which it is required that the effective charge on the O atom of the nucleophile and leaving group, as well as the extent of bonding to the nucleophile and the leaving group, be identical to the TS. It is clear that **4** possesses very little or no phosphorylium character; on the other hand the results point to a concerted mechanism with a TS only slightly on the associative side as in Fig. 3.

### (v) Comparison with some P=S and P=O systems

Part of the comparison of the results of the present study with relevant P=S and P=O systems has already been undertaken above. What is intended here is to situate the findings of the present study alongside trends in the literature in order to highlight the incremental contribution of this work to the discussion of nucleophilic reactivity at P centers.

The hydrolysis of $Me_2P(S)$–OPhX,[35,36] MePhP(S)–OPhX,[35] and $Ph_2P(S)$–OPhX[11d] correlates satisfactorily with $\sigma$ or $\sigma^{\circ}$ rather than $\sigma^{-}$ values while $\beta_{lg}$ values lying in the range of −0.30 to −0.50 have been reported.[35,36] These observations present a mechanistic ambiguity. Correlation with $\sigma$ or $\sigma^{\circ}$ rather than $\sigma^{-}$ values suggests a stepwise mechanism in which formation of the pentacoordinate intermediate is rate-limiting. On the other hand, $\beta_{lg}$ values of −0.30 to −0.50 are consistent with little-to-moderate separation of the leaving group in the TS of a concerted reaction. It is noted that a strongly basic nucleophile and a strongly basic (*i.e.* very poor) leaving group could conceivably move the TS towards the top left-hand corner of Fig. 3. Further experimentation involving Brønsted-type correlations of the type reported in this paper could help clarify issues regarding these substrates.

Activation parameters, solvent effects and divalent metal ion effects on the hydrolysis of the mono/dianions of **2** have been reported; the results implicate a thiometaphosphate intermediate.[3b] It is possible that the unfavorable electrostatic interactions between the nucleophile and anionic forms of **2**, and assistance of leaving group expulsion by the oxyanions in **2**, combine to move the TS towards the bottom right-hand corner of Fig. 3, away from the pentacoordinate intermediate and concerted pathways. Both of these effects are absent with **1**.

A wide spectrum of mechanistic possibilities exist in phosphoryl group transfers. Reaction *via* the metaphosphate intermediate occurs under certain conditions;[13a–c] the presence of the pentacoordinate intermediate when the transfer is between strong nucleophiles[13e,14b,41,42] and reaction *via* the concerted mechanism[7,16,40,41] have been variously demonstrated. P=O substrates reported in the literature which bear the closest structural resemblance to **1** and which have been shown to react with phenoxides are $(EtO)_2P(O)$–OPhX,[7a,34] $(PhO)_2P(O)$–OPhX,[7a] and (to a certain extent) $Ph_2P(O)$–OPhX.[7b] Roughly speaking, the same extent of bond-making occurs in the TS of the concerted reaction of **1** as in these substrates. Conversely, these substrates show greater P–O bond cleavage than **1**. We can speculate, within the scope of literature data available, that P=O and P=S substrates are more likely to react with phenoxides *via* a concerted mechanism, unless special structural and/or environmental circumstances dictate otherwise. There could, however, be wide variations in extents of bond-making and bond cleavage, looseness or tightness of the TS, greater resemblance of the TS to a metaphosphate or pentacoordinate intermediate, depending on the specific substrate and reaction conditions.

P=O substrates are more reactive than their P=S counterparts by two or more orders of magnitude.[43] This order of reactivity has been ascribed to one or more of the following: (i) poorer electron-donating ability of the thioanion relative to the oxyanion in expelling the leaving group;[11d] (ii) the superior ability of O over S to stabilize the developing positive charge at the P center;[11d] (iii) lower electrophilicity of P in P=S relative to P=O due to electronegativity differences, favouring O over S;[43] (iv) differences in the degree of polarization of thiophosphoryl and phosphoryl bonds, favouring the latter;[43c] and (v) structural differences between P=O and P=S moieties, to include interatomic distances and van der Waals radii.[44] The absence of significant phosphorylium ion character in the TS of the concerted reaction of **1** with phenoxides provides support for the low electrophilicity of P in P=S substrates.

The concerted transfer of $(EtO)_2P(O)$ between two $PhO^{-}$ moieties shows significantly greater pentacoordinate intermediate character than the symmetrical reaction of **1**. Assuming that the electronic effects of ethoxy and methoxy groups on (thio)phosphoryl transfer are roughly the same, then the differ-

‡ The symbol $\alpha'$ is used here for the Leffler index so as to avoid duplication with $\alpha$-effect; however it is noted that the original notation for the Leffler index was in fact $\alpha$.

ence in the TS structures of the symmetrical reactions of **1** and $(EtO)_2P(O)$–OPhX can be ascribed to the higher basicity of $PhO^-$ over 3-$CH_3$,4-$NO_2PhO^-$ and the differences in P=O and P=S moieties, in terms of stabilization of the incoming negative charge and associated effects noted above.

## Experimental

### Materials

Reagents and solvents were commercial products used as received unless otherwise noted. Stock solutions of substrates were prepared under $N_2$ and stored in volumetric flasks which were sealed with rubber septa, wrapped with aluminium foil and kept in a refrigerator. Melting points (uncorrected) were obtained with a Thomas-Hoover mp apparatus. An Accumet 825 MP pH meter with a glass electrode calibrated with standard buffer solutions was used to measure pH. NMR spectra were obtained on a Bruker 400 spectrometer operating at 400 MHz. Kinetic experiments were performed on one of the following UV–visible spectrophotometers: Varian Cary 3 double beam, Hewlett Packard 8452A diode ray or Perkin-Elmer Lambda-5. Water was distilled, deionized, degassed and filtered through a 0.22 μm filter. Commercial 1,4-dioxane was distilled from anhydrous stannous chloride to remove peroxides, followed by redistillation from sodium ribbon. Hydrogen peroxide was standardized by the persulfate method.[45] Phenol, 4-chloro- and 4-cyanophenol were recrystallized from petroleum ether (30–60), while butane-2,3-dione monoxime was recrystallized from chloroform. NaOH was purified according to the method of Perrin and Armarego.[46]

*O*,*O*-Dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate, **1**, was a gift from Sumitomo Chemical Co. and was purified by column chromatography;[47] its purity was checked by $^1H$ and $^{31}P$ NMR as well as by GC–MS. The *O*,*O*-dimethyl thiophosphate esters **3a–c** were prepared by a modification of the literature method.[47] **3a** was chromatographed on a silica gel column (230–400 mesh) with 15% EtOAc–85% $CH_2Cl_2$ as eluent; it is an oily liquid with very high bp. **3b** was recrystallized from methanol; mp 52.5–53.5 °C (lit.[48] 53 °C). **3c** is a new compound purified by column chromatography (silica gel 240–400 mesh) with 10% $CH_2Cl_2$–90% hexane as eluent; mp 36.5–37.0 °C (Found: C, 32.42; H, 3.07; N, 4.75. Calc. for $C_8H_9NO_5PSCl$: C, 32.28; H, 3.05; N, 4.71%). The purity of these esters was checked by TLC and GC–MS; they were further characterized by $^1H$, $^{13}C$ and $^{31}P$ NMR. Details of the NMR spectra are given elsewhere.[49]

### Kinetic measurements

The reaction with $HO^-$ as nucleophile was carried out in a NaOH–NaCl solution[50] in the pH range 10.9–12.1. For nucleophiles other than $HO^-$, self-buffered solutions of the nucleophiles were obtained by partially neutralizing the conjugate acid of the relevant nucleophile (NuH) with NaOH such that 2:1 NuH:nucleophile resulted. Injection of varying amounts of the nucleophile stock solution into UV cuvettes containing pure $CO_2$-free water, to which calculated amounts of NaCl had been introduced to maintain constant ionic strength, provided the desired nucleophile concentration for the kinetic run.

Reaction was initiated by injecting 20 μL of a stock solution ($9.54 \times 10^{-3}$ M) of **1** into a 1 cm cuvette containing the desired concentration of the appropriate nucleophile which had been equilibrated thermally at 25.0 ± 0.2 °C in the cell-holder of the spectro-photometer for about 30 min; the nucleophile concentration was at least 50 times greater than the substrate concentration. Reactions were generally followed for 10 half-lives at 398 nm, measuring the formation of 3-methyl-4-nitrophenoxide. Experimental absorbances at "infinite" time were in excellent agreement with calculated ones. The ionic strength of the reaction medium was maintained at 0.3 M with NaCl.[7a] Pseudo first-order rate constants, $k_{obs}$, were obtained by the least squares method as slopes of plots of $\ln(A_{oo} - A_t)$ *vs*. time which showed excellent linearity over 3 half-lives in all cases. The relevant second-order rate constants, $k_{Nu}$, were obtained by application of eqn. (1). In the case of the nucleophiles 2,4,5-$Cl_3$-$PhO^-$ and 2,3,5,6-$F_4$-$PhO^-$ (see entries 8 and 9 in Table 1) whose rates of reaction were very slow, rates were followed up to *ca*. 10% of the total reaction and the second-order rate constants were determined by the initial rate method;[51] the reaction medium was not maintained at constant ionic strength[7a] in such cases. For all the reactions, initial repetitive scans were first carried out prior to the kinetic determination in order to obtain the appropriate wavelength for monitoring the appearance of the product 3-methyl-4-nitrophenoxide, 398 nm in all cases, as well as to ensure the occurrence of isosbestic points which exclude the presence of any long-lived intermediate with significant absorption along the reaction pathway.

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